

Testing the Mean Matrix in High-Dimensional Transposable Data

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Abstract

The structural information in high-dimensional transposable data allows us to write the data recorded for each subject in a matrix such that both the rows and the columns correspond to variables of interest. One important problem is to test the null hypothesis that the mean matrix has a particular structure without ignoring the dependence structure among and/or between the row and column variables. To address this, we develop a generic and computationally inexpensive nonparametric testing procedure to assess the hypothesis that, in each predefined subset of columns (rows), the column (row) mean vector remains constant. In simulation studies, the proposed testing procedure seems to have good performance and, unlike simple practical approaches, it preserves the nominal size and remains powerful even if the row and/or column variables are not independent. Finally, we illustrate the use of the proposed methodology via two empirical examples from gene expression microarrays.

Keywords— High-dimensional transposable data; Hypothesis testing; Mean matrix; Nonparametric test.

1 Introduction

In some applications, the measurements related to each subject are naturally organized in a matrix, especially when the rows and columns correspond to two different sets of variables and dependencies are expected to occur between and/or among them. Allen and Tibshirani (2010) introduced the term ‘transposable data’ to acknowledge the structural information and the presence of two-way dependencies in matrix-valued random variables. Examples of transposable data can be found in spatiotemporal studies (Genton, 2007; Mardia and Goodall, 1993), in cross-classified multivariate data (Galecki, 1994; Naik and Rao, 2001), in genetics (Allen and Tibshirani, 2010, 2012; Efron, 2009; Teng and Huang, 2009; Yin and Li, 2012; Ning and Liu, 2013), in functional MRI (Allen and Tibshirani, 2010), in time-series (Carvalho and West, 2007; Lee et al., 2013) and in electroencephalography studies (Zhang et al., 1995) among others.

Although our findings can be applied to any of the disciplines mentioned above, our work is primarily motivated by biological studies that use microarrays to study gene expression patterns in multiple tissue samples taken from the same subject (Sottoriva et al., 2013; Zahn et al., 2007). For each subject, the row variables correspond to genes, the column variables to tissue samples and the measurements are mRNA gene expression levels. A complex and high-dimensional dependence structure is expected to occur as neither the genes nor the tissue samples are likely to be independent. In such studies, a natural biological objective is to determine whether given subsets of tissue samples share a common mean vector of gene expression levels. This leads to two important statistical challenges. First, the number of genes will typically exceed the number of subjects and it is a well known fact that classical

multivariate tests for testing equality of mean vectors, such as the Hotelling's T^2 or Wilk's Λ , are not applicable in 'large p , small N ' settings. Second, the dependence among the tissue samples for each subject might restrict us from utilizing practical approaches that rely on mixing univariate standard testing procedures and multiple testing correction methods. This includes, for example, the approach of testing the significance of each gene across tissue samples based on an analysis of variance (ANOVA) test and adjusting the corresponding p -values for multiple testing. This approach requires tissue-wise (column-wise) independence, a rather strong assumption that is unlikely to be met in real datasets.

To introduce these concepts in mathematical terms, suppose that an experimentalist collects N independent and identically distributed (i.i.d.) transposable $r \times c$ random matrices $\mathbf{X}_1, \dots, \mathbf{X}_N$. For each subject, there are r row variables and c column variables and the high-dimensional setting is indicated by letting the sample size (N) be much smaller than the number of observations (rc) for a single subject. The goal is to perform hypothesis testing for $\mathbf{M} = E[\mathbf{X}_i]$, the $r \times c$ mean matrix of the transposable data, while accounting for the two-way dependencies.

To illustrate some difficulties of this task, consider the simple hypothesis

$$H_0 : \mathbf{M} = \boldsymbol{\mu} \mathbf{1}_c^T \text{ vs. } H_1 : \mathbf{M} \neq \boldsymbol{\mu} \mathbf{1}_c^T, \quad (1)$$

where $\boldsymbol{\mu}$ is an unknown r -variate parameter vector and $\mathbf{1}_s$ denotes an s -variate vector of ones. The null hypothesis suggests that the mean relationship between the row and column variables is completely determined by the row variables. In the motivating examples, H_0 in (1) is consistent with no genes showing differential expression across the multiple tissue samples. To the best of our knowledge, no statistical procedure exists to test hypothesis (1) directly in high-dimensional transposable data unless there are only two dependent column variables ($c = 2$). In this case, the test proposed by Chen and Qin (2010) for comparing the mean vector of paired high-dimensional random vectors can be used. To accomplish this, one needs to form the vector of the difference of the two columns for each subject and then test the hypothesis of a zero mean vector. Unfortunately, there is no straightforward way to apply or extend this test when $c > 2$. In particular, attempts to do this essentially infer rather than test the mean relationship between the row and column variables. For example, suppose that $\mathbf{M} = [\boldsymbol{\mu}, -\boldsymbol{\mu}, \boldsymbol{\mu}, -\boldsymbol{\mu}]$ and consider the following naive algorithm to test hypothesis (1). First, create two groups of column variables, one based on the first two columns and the other based on the last two. Second, for each group create N r -variate random vectors by averaging the appropriate columns in each matrix, and then for each subject create the r -variate vectors of the difference of the two groups. Thirdly, test hypothesis (1) using the test statistic of Chen and Qin (2010) as above. It can be shown that this vector-based test statistic will be powerless since the transformed random vectors will indeed have a zero mean vector.

By contrast, we propose a simple approach to test hypothesis (1) that overcomes these theoretical problems. In this direction, let $\mathbf{P}_c = \mathbf{I}_c - \mathbf{J}_c/c$ where \mathbf{I}_s is the identity matrix of size s and \mathbf{J}_s is the $s \times s$ matrix of ones, and let $\text{tr}(\mathbf{A})$ denote the trace operator of the matrix \mathbf{A} . Note that \mathbf{P}_c is a symmetric and idempotent ($\mathbf{P}_c^2 = \mathbf{P}_c$) matrix such that $\text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P}_c) = 0$ if and only if H_0 in (1) holds. Since the Frobenius norm, $\text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P}_c)$, measures deviations from H_0 in (1), it seems meaningful to develop a test statistic based on $\sum_{i \neq j} \text{tr}(\mathbf{X}_i^T \mathbf{X}_j \mathbf{P}_c) / [N(N-1)]$, the unbiased estimator of this norm. Under rather weak conditions about the two-way dependence structure, illustrated in Section 2.3, this estimator asymptotically follows a normal distribution, and hence, the critical region of the test statistic can be defined under H_0 .

The main contribution of this paper is that we allow testing more complicated hypotheses than hypothesis (1) for the mean matrix. In particular, we consider the hypothesis

$$H_0 : \mathbf{M} = [\boldsymbol{\mu}_1 \mathbf{1}_{c_1}^T, \boldsymbol{\mu}_2 \mathbf{1}_{c_2}^T, \dots, \boldsymbol{\mu}_g \mathbf{1}_{c_g}^T] \text{ vs. } H_1 : \mathbf{M} \neq [\boldsymbol{\mu}_1 \mathbf{1}_{c_1}^T, \boldsymbol{\mu}_2 \mathbf{1}_{c_2}^T, \dots, \boldsymbol{\mu}_g \mathbf{1}_{c_g}^T], \quad (2)$$

where c_1, \dots, c_g are positive integers such that $\sum_{q=1}^g c_q = c$ with at least one $c_q \geq 2$ and $\boldsymbol{\mu}_1, \dots, \boldsymbol{\mu}_g$ are g unknown r -variate parameter vectors. H_0 in (2) states that in each one of the given g column groups there is no column effect upon the mean of the row variables. Since g is known but arbitrary, the proposed testing procedure is not bounded by the number of column groups or the group size under consideration. For example, hypothesis (1) is a special case of hypothesis (2) with $g = 1$ and $c_1 = c$ while the hypothesis that two column variables, say the first two, have a common mean vector

is obtained by setting $g = c - 1$, $c_1 = 2$ and $c_2, \dots, c_g = 1$. Similarly to testing hypothesis (1), the proposed test statistic will be based on an asymptotic argument via a pivotal quantity that is the unbiased estimator of the distance of the mean matrix from H_0 in (2). The proposed testing methodology is a global procedure that produces a single p -value for testing H_0 in (2) and it is not seriously restricted by the presence of dependence structures other than the independence.

The proposed testing procedure can also be employed to determine the mean relationship between row and column variables in many predefined sets of row variables rather than across all row variables. In the motivating examples, the biological interest might lie in finding gene-sets for which the mean vector of expression levels varies across different tissue samples. This could allow better identification of biological processes that are tissue-specific, thus facilitating their exploration in greater detail. In this case, one needs to test hypothesis (1) for each predefined gene-set and then correct the corresponding p -values for multiple testing. We illustrate how to perform this type of analysis in Section 4.1.

The rest of this article is structured as follows. In Section 2, we introduce the high-dimensional working framework and we construct the test statistic for testing hypothesis (2). We also discuss the asymptotic power of the proposed test, we argue that the required assumptions that make the high-dimensional setting manageable are weak, we make general comments about practical aspects of the testing procedure and we provide guidelines about how to adjust the proposed methodology to test hypotheses other than hypothesis (2). In Section 3, we examine the performance of the proposed testing methodology in finite samples using simulations. In Section 4, we apply the proposed testing methodology to two microarrays studies where gene expression levels are measured in different tissue samples (Sottoriva et al., 2013; Zahn et al., 2007). In Section 5, we summarize the main findings of our research and future research directions.

2 Test Statistics for the Mean Matrix

As the generative process for transposable data, consider a matrix-valued extension of the nonparametric model for vectors considered in Bai and Saranadasa (1996) and Chen and Qin (2010)

$$\mathbf{X}_i = \mathbf{W}_i + \mathbf{M} \quad (3)$$

for $i = 1, \dots, N$, where

1. $\mathbf{M} = E[\mathbf{X}_i]$ is the $r \times c$ mean matrix,
2. \mathbf{W}_i is an $r \times c$ matrix of random variables such that $\text{vec}(\mathbf{W}_i) = \Sigma^{1/2} \text{vec}(\mathbf{Z}_i)$, and where $\text{vec}(\mathbf{A})$ denotes vectorization of the matrix \mathbf{A} ,
3. $\Sigma = \Sigma^{1/2} \Sigma^{1/2} = \text{cov}[\text{vec}(\mathbf{X}_i)]$ is an $(rc) \times (rc)$ positive-definite covariance matrix,
4. $\mathbf{Z}_1, \dots, \mathbf{Z}_N$ are i.i.d. $r \times c$ random matrices and Z_{iab} is the (a, b) -th element of \mathbf{Z}_i ,
5. $E[Z_{iab}] = 0$, $E[Z_{iab}^2] = 1$, $E[Z_{iab}^4] = 3 + B$ for a finite constant $B > -2$, $E[Z_{iab}^8] < \infty$ and for any positive integers l_1, \dots, l_q with $\sum_{\nu=1}^q l_\nu \leq 8$

$$E[Z_{ia_1 b_1}^{l_1} Z_{ia_2 b_2}^{l_2} \dots Z_{ia_q b_q}^{l_q}] = E[Z_{ia_1 b_1}^{l_1}] E[Z_{ia_2 b_2}^{l_2}] \dots E[Z_{ia_q b_q}^{l_q}]$$

$$\text{for } (a_1, b_1) \neq (a_2, b_2) \neq \dots \neq (a_q, b_q).$$

The matrix-variate normal distribution (Dawid, 1981; Gupta and Nagar, 2000), a common and sensible choice for modeling transposable data, is a special case of model (3). To see this, let Z_{iab} be i.i.d. random variables from a standard normal distribution $N(0, 1)$ and let $\Sigma = \Sigma_2 \otimes \Sigma_1$, where Σ_1 is the covariance matrix of the row variables, Σ_2 is the covariance matrix of the column variables and \otimes denotes the Kronecker product operator applied to matrices. However, we underline that model (3) is more general. It can handle departures from the matrix-variate normal model by relaxing the normality and/or the covariance structure assumption. The distribution of the “white-noise” random variables in \mathbf{Z}_i remains unspecified. In fact, the white noise random variables do not need to be

independent or identically distributed. Also the dependence structure between and among the row and column variables is not limited to a Kronecker product form.

To construct the test statistic for testing hypothesis (2), we need additional notation. Let $\mathbf{P}_{\{c_1, c_2, \dots, c_g\}} = \text{diag}(\mathbf{P}_{c_1}, \mathbf{P}_{c_2}, \dots, \mathbf{P}_{c_g})$ be the $c \times c$ block diagonal matrix where the positive integers $\{c_1, c_2, \dots, c_g\}$ are defined by H_0 in (2). For notational ease, suppress the index set in $\mathbf{P}_{\{c_1, c_2, \dots, c_g\}}$ and write instead \mathbf{P} . Further, note that \mathbf{P} is a projection matrix as it is both idempotent and symmetric. The key to our proposal is to observe that $\text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P}) = 0$ if and only if H_0 in (2) holds. To see this, note that $\text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P}) = \text{tr}(\mathbf{P} \mathbf{M}^T \mathbf{M})$ is the sum of squares of the elements of $\mathbf{M} \mathbf{P}$, whose (a, b) -th element equals the difference between μ_{ab} , the (a, b) -th element of \mathbf{M} , and $\bar{\mu}_a^{(k)}$, the average of the a -th row in the mean matrix when this is restricted to the column group, say k , to which column b belongs under H_0 in (2). Therefore, it is sensible to consider the unbiased estimator of $\text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P})$

$$G_N = \frac{1}{N(N-1)} \sum_{i \neq j} \text{tr}(\mathbf{X}_i^T \mathbf{X}_j \mathbf{P}),$$

whose variance is

$$\text{Var}[G_N] = \frac{2}{N(N-1)} \text{tr}([\Sigma(\mathbf{P} \otimes \mathbf{I}_r)]^2) + \frac{4}{N} \text{vec}(\mathbf{M} \mathbf{P})^T \Sigma \text{vec}(\mathbf{M} \mathbf{P}).$$

Next, we define the asymptotic framework needed to derive the limiting distribution of G_N . We handle the high-dimensional setting without specifying the limiting rate of the pairwise ratios of the triplet (N, r, c) because in many applications, including our motivating examples, the number of row (genes) and/or column (multiple samples) variables are not expected to increase proportionally to the sample size. Instead, we assume that as $N \rightarrow \infty$ and $rc = r(N)c(N) \rightarrow \infty$, the following conditions hold:

$$\text{tr}([\Sigma(\mathbf{P} \otimes \mathbf{I}_r)]^4) = o\{\text{tr}^2([\Sigma(\mathbf{P} \otimes \mathbf{I}_r)]^2)\} \quad (4)$$

and

$$\text{vec}(\mathbf{M} \mathbf{P})^T \Sigma \text{vec}(\mathbf{M} \mathbf{P}) = o\left\{\frac{1}{N} \text{tr}([\Sigma(\mathbf{P} \otimes \mathbf{I}_r)]^2)\right\} \quad (5)$$

or

$$\frac{1}{N} \text{tr}([\Sigma(\mathbf{P} \otimes \mathbf{I}_r)]^2) = o\{\text{vec}(\mathbf{M} \mathbf{P})^T \Sigma \text{vec}(\mathbf{M} \mathbf{P})\}. \quad (6)$$

The assumption $rc \rightarrow \infty$ does not require $r \rightarrow \infty$ and $c \rightarrow \infty$ simultaneously and it allows the number of row or column variables to be fixed provided that the other dimension of the transposable data tends to ∞ . Condition (4) specifies the class of covariance matrices for Σ under consideration. In Section 2.3, we argue that this class is quite large and thus, the proposed testing procedure is not seriously restricted. At least one of the conditions (5) and (6) is needed to control the asymptotic variance of G_N and to derive the asymptotic distribution of G_N , given in Theorem 1 and proven in the Web Appendix A.

Theorem 1 *Under the nonparametric model (3), condition (4) and either condition (5) or condition (6)*

$$\frac{G_N - \text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P})}{\sqrt{\text{Var}[G_N]}} \rightsquigarrow N(0, 1)$$

where \rightsquigarrow denotes convergence in distribution as $N \rightarrow \infty$ and $rc = r(N)c(N) \rightarrow \infty$. Consequently, under H_0 in (2),

$$\frac{G_N}{\sqrt{2 \text{tr}([\Sigma(\mathbf{P} \otimes \mathbf{I}_r)]^2) / [N(N-1)]}} \rightsquigarrow N(0, 1).$$

To construct the test statistic, we avoid estimating the unknown and high-dimensional covariance matrix Σ upon observing that the N i.i.d. rc -variate random vectors $\mathbf{Y}_i = \text{vec}(\mathbf{X}_i \mathbf{P})$ have covariance

matrix $\mathbf{\Omega} = (\mathbf{P} \otimes \mathbf{I}_r)\mathbf{\Sigma}(\mathbf{P} \otimes \mathbf{I}_r)$ and that $\text{tr}(\mathbf{\Omega}^2) = \text{tr}([\mathbf{\Sigma}(\mathbf{P} \otimes \mathbf{I}_r)]^2)$. Therefore, it follows from the work of Chen, Zhang, and Zhong (2010) that

$$T_N = \frac{1}{D_2^N} \sum_{i \neq j} (\mathbf{Y}_i^T \mathbf{Y}_j)^2 - 2 \frac{1}{D_3^N} \sum_{i \neq j \neq k}^* \mathbf{Y}_i^T \mathbf{Y}_j \mathbf{Y}_i^T \mathbf{Y}_k + \frac{1}{D_4^N} \sum_{i \neq j \neq k \neq l}^* \mathbf{Y}_i^T \mathbf{Y}_j \mathbf{Y}_k^T \mathbf{Y}_l$$

where $D_t^s = (s-t)!/s!$ and \sum^* denotes summation over mutually exclusive indices, is a ratio-consistent estimator of $\text{tr}(\mathbf{\Omega}^2)$. Therefore, the proposed test rejects H_0 in (2) with an α significance level if and only if

$$G_N^* = \frac{G_N}{\sqrt{2T_N/[N(N-1)]}} \geq z_\alpha,$$

where z_α is the upper α -quantile of $N(0, 1)$.

2.1 Remarks

Consider the transformation $\mathbf{X}_i \mapsto a\mathbf{A}\mathbf{X}_i + \mathbf{C}$ where $a \neq 0 \in \mathfrak{R}$, \mathbf{A} is an $r \times r$ orthogonal matrix and \mathbf{C} is an $r \times c$ matrix of constants such that $\mathbf{C}\mathbf{P} = \mathbf{0}_{r \times c}$, and where $\mathbf{0}_{s \times t}$ denotes the zero matrix of size $s \times t$. As desired, the test statistic G_N^* is invariant to orthogonal rotations of the row variables, to scalar multiplication, and to location shifts of the mean matrix under H_0 in (2). The last property implies that the nominal size of the test statistic is not affected by the magnitude of the true mean matrix \mathbf{M} given that this satisfies H_0 in (2). To this end, note that column groups of size one do not contribute to the test statistic, meaning that the value of G_N^* does not change if column groups of size one ($c_k = 1$) are ignored. This is not surprising since no mean comparisons are performed therein. Hence, these column variables should be removed prior to calculating the test statistic.

Although the testing methodology is presented for testing the mean structure of row variables across groups of column variables, we emphasize that the same testing procedure can be used to test the mean structure of column variables across groups of row variables. To do this, apply the transformation $\mathbf{X}_i \mapsto \mathbf{X}_i^T$ prior to calculating G_N^* .

A critical point in our proposal is the choice of the projection matrix \mathbf{P} . Although Theorem 1 holds for any projection matrix that satisfies the required assumptions, say \mathbf{P}^* , to avoid trivial power under certain alternatives it is essential to require that $\mathbf{M}\mathbf{P}^* = \mathbf{0}_{r \times c}$ if and only if the corresponding null hypothesis is true. For example, an alternative way to test hypothesis (1) is to consider the projection matrix $\mathbf{P}^* = \mathbf{J}_c/c$ (instead of $\mathbf{P}_c = \mathbf{I}_c - \mathbf{J}_c/c$). The asymptotic power of the resulting test statistic is trivial if, for example, c is even and the mean vector is $\boldsymbol{\mu}$ for the odd columns of \mathbf{M} and $-\boldsymbol{\mu}$ for the even columns. Thus attention is required when projection matrices other than the suggested ones are used.

It is important to note that the testing procedure can be modified and applied to test hypotheses other than hypothesis (2). For example, consider testing the hypothesis of a known $r \times c$ matrix of constants \mathbf{M}_0 ($H_0 : \mathbf{M} = \mathbf{M}_0$). To do this, we can center the data by subtracting \mathbf{M}_0 and then employ the test statistic G_N^* calculated using $\mathbf{P} = \mathbf{I}_c$. Another example is testing the hypothesis $H_0 : \boldsymbol{\mu}_1 - \boldsymbol{\mu}_2 = \boldsymbol{\mu}_0$, where $\boldsymbol{\mu}_1$ and $\boldsymbol{\mu}_2$ are the unknown r -variate mean vectors of the first and second column variable respectively, and $\boldsymbol{\mu}_0$ is an r -variate vector of known constants. To accomplish this, one needs to subtract $\boldsymbol{\mu}_0$ from the first column of each data matrix and then test hypothesis (2) with $g = 2$, $c_1 = 2$ and $c_2 = \dots = c_g = 1$ using the transformed data. In a similar way, the proposed method can be extended to test known differences in the mean vectors of two or more column groups.

To calculate T_N , it is more efficient to use the equivalent formula given in Himeno and Yamada (2014) which reduces the computational cost from $O(N^4)$ to $O(N^2)$. Combining this result with simple algebraical properties for the trace operator, we can prove that the proposed testing methodology is computationally cheap regardless of the dimensionality, i.e., number of row variables, number of column variables or sample size.

2.2 Asymptotic power

Under condition (5), the leading order power for the proposed test is

$$\beta_N = \Phi \left(-z_a + N \frac{\text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P})}{\sqrt{2\text{tr}(\mathbf{\Omega}^2)}} \right),$$

where Φ is the cumulative distribution function of $N(0, 1)$. The power of the proposed test is bounded since

$$\Phi \left(-z_a + N \frac{\text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P})}{\sqrt{2\text{tr}(\mathbf{\Sigma}^2)}} \right) \leq \beta_N \leq \Phi \left(-z_a + N \frac{\text{tr}(\mathbf{M}^T \mathbf{M})}{\sqrt{2\text{tr}(\mathbf{\Omega}^2)}} \right),$$

and thus a sufficient condition for the proposed test to have non-trivial power is

$$\lim_{N, (rc) \rightarrow \infty} N \frac{\text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P})}{\sqrt{2\text{tr}(\mathbf{\Sigma}^2)}} > 0.$$

Under condition (6), the leading order power term becomes

$$\beta_N = \Phi \left(\frac{\sqrt{N} \text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P})}{2\sqrt{\text{vec}(\mathbf{M} \mathbf{P})^T \mathbf{\Sigma} \text{vec}(\mathbf{M} \mathbf{P})}} \right) = \Phi \left(\frac{\sqrt{N} \text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P})}{2\sqrt{\text{vec}(\mathbf{M})^T \mathbf{\Omega} \text{vec}(\mathbf{M})}} \right).$$

The power of the proposed test remains bounded since

$$\Phi \left(\frac{\sqrt{N} \text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P})}{2\sqrt{\text{vec}(\mathbf{M})^T \mathbf{\Sigma} \text{vec}(\mathbf{M})}} \right) \leq \beta_N \leq \Phi \left(\frac{\sqrt{N} \text{tr}(\mathbf{M}^T \mathbf{M})}{2\sqrt{\text{vec}(\mathbf{M})^T \mathbf{\Omega} \text{vec}(\mathbf{M})}} \right),$$

which implies that

$$\lim_{N, (rc) \rightarrow \infty} \frac{\sqrt{N} \text{tr}(\mathbf{M}^T \mathbf{M} \mathbf{P})}{2\sqrt{\text{vec}(\mathbf{M})^T \mathbf{\Sigma} \text{vec}(\mathbf{M})}} > 0$$

is a sufficient condition for the proposed test to have non-trivial power.

Although the proposed testing procedure can handle dependence structures other than the independence, it can still be more powerful than typical univariate tests that require multiple testing corrections even for independent row and column variables ($\mathbf{\Sigma} = \mathbf{I}_{rc}$). To provide such an instance, assume a fixed number of column variables and no row-effect in the mean structure, that is $M_{ab} = M_b$ where M_{ab} is the (a, b) -th element of \mathbf{M} . In this scenario, the asymptotic power of the proposed test under conditions (5) and (6) becomes

$$\Phi \left(-z_a + \sqrt{\frac{N^2 r}{2(c-g)}} \sum_{k=1}^g \sum_{b=c_{k-1}+1}^{c_k} (M_b - \bar{M}^{(k)})^2 \right) \text{ and } \Phi \left(\frac{r}{2} \sqrt{N \sum_{k=1}^g \sum_{b=c_{k-1}+1}^{c_k} (M_b - \bar{M}^{(k)})^2} \right)$$

respectively, where $c_0 = 0$ and $\bar{M}^{(k)}$ is the average of the mean of the row variable a in group k . As desired, under either (5) or (6), the power of the test is an increasing function of the number of row variables r . On the contrary, the power of some commonly used univariate tests applied sequentially to each row, such as ANOVA based tests, depends on the magnitude of the differences $\{M_b - \bar{M}^{(k)}, b = 1, \dots, c\}$. Therefore, we expect ANOVA based tests to suffer from low power when these differences are small regardless of r . Note that we reach to the same conclusion even if we replace the no row-effect in the mean structure with an unstructured one such that all row-wise differences $\{M_{ab} - \bar{M}^{(ak)}, b = 1, \dots, c\}$ are small, and where $\bar{M}^{(ak)}$ denotes the average of the mean of the row variable a in group k . In these cases, the proposed test performs better because it extracts information from both the row and the column variables, which is ignored by univariate tests. We verified this speculation in simulations where we also investigated the situation in which the null hypothesis under consideration was violated for varying proportions of the rows in the mean matrix.

2.3 Class of covariance matrices under consideration

We provide examples of covariance matrices that satisfy condition (4) and technical details can be found in Web Appendix C. Because of the popularity of the matrix-variate normal distribution in modelling transposable data, we first study the implications of condition (4) when $\Sigma = \Sigma_2 \otimes \Sigma_1$. In this case, condition (4) becomes

$$\text{tr}[(\mathbf{P}\Sigma_2)^4] \text{tr}(\Sigma_1^4) = o\{\text{tr}^2[(\mathbf{P}\Sigma_2)^2] \text{tr}^2(\Sigma_1^2)\}.$$

For example, this condition is met if $\text{tr}[(\mathbf{P}\Sigma_2)^4] = o\{\text{tr}^2[(\mathbf{P}\Sigma_2)^2]\}$ and/or if $\text{tr}(\Sigma_1^4) = o\{\text{tr}^2(\Sigma_1^2)\}$. This means that Σ_1 and/or Σ_2 can have bounded eigenvalues or a few eigenvalues that diverge slowly to infinity (Chen and Qin, 2010), or satisfy a (banded) first order autoregressive correlation pattern such that the corresponding variances are bounded away from 0 or ∞ (Chen et al., 2010). When c is fixed, then condition (4) becomes $\text{tr}(\Sigma_1^4) = o\{\text{tr}^2(\Sigma_1^2)\}$, and it follows that Σ_1 cannot satisfy a compound symmetry correlation structure. However, if r is fixed, then condition (4) becomes $\text{tr}[(\mathbf{P}\Sigma_2)^4] = o\{\text{tr}^2[(\mathbf{P}\Sigma_2)^2]\}$, and therefore the compound symmetry correlation structure is an acceptable dependence structure for Σ_2 .

A sufficient assumption for condition (4) in the presence of uncorrelated (not necessarily independent) column variables is that $\text{tr}(\Sigma^4) = o\{\text{tr}^2(\Sigma^2)\}$. This assumption covers the case of independent row and column variables with bounded variances or a few divergent variances among others. When the row and column variables are correlated, then condition (4) is met for a covariance matrix Σ with bounded eigenvalues or a few divergent values that diverge slowly, for Σ that implies a (banded) first order autoregressive correlation pattern or a (banded) compound symmetry correlation matrix.

3 Simulation Studies

We investigated the nominal size and the power of the proposed testing procedure using simulations. The simulated random matrices $\mathbf{X}_1, \dots, \mathbf{X}_N$ satisfied model (3). To study the nonparametric nature of the proposed methodology, three distributional scenarios were considered for the elements of \mathbf{Z}_i :

1. A normality scenario, in which $Z_{iab} \stackrel{i.i.d}{\sim} N(0, 1)$.
2. A centralized gamma distributional scenario, in which $Z_{iab} = (Z_{iab}^* - 8)/4$ and $Z_{iab}^* \stackrel{i.i.d}{\sim} \text{Gamma}(4, 0.5)$.
3. A mixture of Scenarios 1 and 2, in which the random variables in the upper half of \mathbf{Z}_i are distributed as in Scenario 1, while the remaining random variables are distributed as in Scenario 2.

Conditional on N , \mathbf{M} , Σ and the distributional scenario, we draw 1000 replicates while keeping the significance level fixed at 5%. For each competing testing procedure, we calculated the empirical size as the proportion of rejections when $\mathbf{M} = \mathbf{0}_{r \times c}$ and the empirical power as the proportion of rejections when $\mathbf{M} \neq \mathbf{0}_{r \times c}$ as defined in Sections 3.1 and 3.4. To distinguish the test statistics of the proposed methodology used in the simulations, we denoted by $H_{\{c_1, c_2, \dots, c_g\}}$ the test statistic G_N^* of the proposed methodology based on $\mathbf{P}_{\{c_1, c_2, \dots, c_g\}}$. Further, we let $[k]$ denote the integer part of $k \in \mathbb{R}$. Additional simulation studies for the proposed testing methodology can be found on the Web Appendix B.

3.1 Comparison with ANOVA and Kruskal-Wallis

We first compared the proposed testing methodology, evaluated using $H_{\{c\}}$, to the ANOVA test of no group effect and the Kruskal-Wallis test for testing the hypothesis of no column effect in the mean matrix, i.e., testing hypothesis (1). The ANOVA and Kruskal-Wallis tests were applied sequentially to each of the r row variables and the resulting p -values were adjusted using the false discovery rate (FDR) correction and the Bonferroni (BON) correction. Web Table 2 suggests that the ANOVA and Kruskal-Wallis tests are extremely conservative in the presence of row-wise and column-wise dependencies and therefore, a fair and meaningful comparison is ensured by restricting the dependence structure to independent row and column variables ($\Sigma = \mathbf{I}_{rc}$). In addition to calculating the empirical size, we

Table 1: Empirical size and power of $H_{\{10\}}$, ANOVA and Kruskal-Wallis test at 5% significance.

		$H_{\{10\}}$		ANOVA				Kruskal-Wallis			
				FDR		BON		FDR		BON	
r	N	Power	Size	Power	Size	Power	Size	Power	Size	Power	Size
100	10	0.138	0.063	0.051	0.047	0.051	0.046	0.013	0.014	0.013	0.014
	30	0.412	0.057	0.091	0.045	0.088	0.045	0.062	0.040	0.060	0.039
	50	0.756	0.053	0.136	0.045	0.125	0.044	0.115	0.043	0.112	0.043
	100	0.997	0.044	0.319	0.047	0.294	0.045	0.317	0.048	0.285	0.047
500	10	0.186	0.063	0.075	0.066	0.075	0.066	0.011	0.008	0.011	0.008
	30	0.703	0.039	0.096	0.060	0.094	0.059	0.051	0.033	0.047	0.033
	50	0.974	0.040	0.102	0.042	0.093	0.040	0.082	0.026	0.077	0.026
	100	1.000	0.051	0.261	0.054	0.244	0.053	0.253	0.048	0.233	0.047

measured the empirical power of the competing tests assuming that $\mathbf{M} = [\mathbf{0}_{r \times 7}, t\mathbf{J}_{r \times 3}]$ where $\mathbf{J}_{k \times l}$ denotes the $k \times l$ matrix of ones. This configuration is motivated by the power analysis in Section 2.2. The constant t was selected such that $\text{tr}(\mathbf{M}^T \mathbf{M}) / \sqrt{r(c-1)} = 0.1$, i.e., by fixing the quantity that determines the upper bound of the asymptotic power of the proposed tests under condition (5) equal to 0.1. In this way, the asymptotic power of $H_{\{c\}}$ is not trivial and the simulation results are comparable across varying values of r and c . Table 1 displays the results under Scenario 3 - similar patterns were observed under the other two scenarios. Unlike the Kruskal-Wallis test which seemed to be conservative unless $N = 100$, the empirical sizes for $H_{\{c\}}$ and for the ANOVA test appeared to be a good approximation of the nominal size even for $N = 10$. Despite the conservativeness of the proposed test for $N = 10$, it was always more powerful than the ANOVA and the Kruskal-Wallis test. Conditional on N and the distributional scenario, the empirical power of the proposed test increased as r increased while that of the competing testing procedures did not change much even when $N = 100$. This is due to the effectiveness of the proposed test in high-dimensional settings when the magnitude of the row-wise (column-wise) difference in the mean matrix is small but constant for every row (column) of the mean structure.

Next, we compared the empirical power of the competing testing procedures under a sparsity scenario for the mean structure. In particular, we defined $\mathbf{M} = [\mathbf{0}_{r \times 9}, \boldsymbol{\mu}]$ and similarly to Chen and Qin (2010), we let the r -variate vector $\boldsymbol{\mu}$ contain a varying proportion (0%, 25%, 50%, 75%, 95% and 99%) of zero elements. At each proportion level, we employed a linearly increasing allocation where two nonzero-elements of $\boldsymbol{\mu}$ satisfy $\mu_{l_1} < \mu_{l_2}$ if and only if $l_1 < l_2$. We set $r = 100, 500, 1000$ and we let $\boldsymbol{\Sigma} = \mathbf{I}_{10r}$. To make the results comparable across the sampling schemes, the non-zero elements of $\boldsymbol{\mu}$ were defined in such a way that

$$\frac{\text{tr}(\mathbf{M}^T \mathbf{M})}{\sqrt{r(c-1)}} = 0.15.$$

Table 2 displays the simulation results only for $r = 1000$ under Scenario 3 since similar trends were noted for the remaining sampling schemes. As desired, the empirical power of the proposed methodology appeared to be unaffected by the proportion of zero elements in $\boldsymbol{\mu}$ for fixed N and the empirical power approached 1.00 as soon as $N = 50$. However, the empirical power of the ANOVA and Kruskal-Wallis tests seemed to decrease as the proportion of zero elements decreased. In fact, the largest differences between the empirical power of the proposed test and of the univariate tests were observed when there were no zeros in $\boldsymbol{\mu}$. This agrees with our claims in Section 2.2 regarding the power of the competing procedures. For 1% of non-zero elements in $\boldsymbol{\mu}$, the empirical powers of the three testing procedures were comparable unless $N = 30$ in which case the ANOVA and Kruskal-Wallis tests were substantially more powerful than the proposed test. For all other proportions of zero elements in $\boldsymbol{\mu}$, the proposed test was extremely more powerful than the univariate tests with the sole exception of the sampling scheme with $N = 100$ and 75% of zero elements in $\boldsymbol{\mu}$. Overall, the proposed test appeared to be more powerful than univariate tests under the sparsity scenario for the mean matrix and under the rather unrealistic assumption of independent row and column variables for the dependence structure.

Table 2: Empirical power of $H_{\{10\}}$, ANOVA and Kruskal-Wallis for the sparsity scenario with $r = 1000$ under Scenario 3 at 5% significance

N	$\#\{\mu_l = 0\}$	$H_{\{10\}}$	ANOVA		Kruskal-Wallis	
			FDR	BON	FDR	BON
10	99%	0.164	0.189	0.184	0.014	0.014
	95%	0.170	0.068	0.067	0.003	0.003
	75%	0.162	0.062	0.061	0.003	0.003
	50%	0.164	0.061	0.060	0.003	0.003
	25%	0.161	0.061	0.060	0.004	0.004
	0 %	0.168	0.058	0.057	0.003	0.003
30	99%	0.618	0.997	0.997	0.976	0.971
	95%	0.624	0.254	0.242	0.132	0.125
	75%	0.618	0.096	0.091	0.052	0.050
	50%	0.626	0.082	0.080	0.044	0.043
	25%	0.628	0.081	0.078	0.047	0.045
	0 %	0.625	0.084	0.081	0.051	0.049
50	99%	0.949	1.000	1.000	1.000	1.000
	95%	0.948	0.721	0.678	0.566	0.538
	75%	0.949	0.144	0.135	0.103	0.100
	50%	0.943	0.117	0.108	0.080	0.078
	25%	0.944	0.105	0.102	0.078	0.077
	0 %	0.944	0.094	0.092	0.076	0.073
100	99%	1.000	1.000	1.000	1.000	1.000
	95%	1.000	1.000	1.000	1.000	0.999
	75%	1.000	0.398	0.356	0.314	0.290
	50%	1.000	0.245	0.229	0.192	0.176
	25%	1.000	0.197	0.180	0.157	0.148
	0 %	1.000	0.163	0.152	0.155	0.142

Similar trends were observed for an equal allocation scenario in μ (see Web Table 3).

3.2 Comparison with the Chen-Qin test

Suppose we want to test hypothesis (1) when the column variables are independent. In this case, we can create c groups, one group for each column variable that contains N independent r -variate random vectors. An alternative practical approach to test hypothesis (1) is to apply the two-sample test for high-dimensional mean vectors proposed by Chen and Qin (2010) to all possible pairs of groups, and then adjust the resulting p -values for multiple testing. To satisfy the required assumptions of the Chen-Qin test, Σ was set equal to a block diagonal matrix with c blocks. Each block of Σ satisfied a first-order autoregressive form ($\{\rho^{|a-b|}\}_{1 \leq a, b \leq r}$) where $\rho = 0.5$ in the first $c/2$ blocks and $\rho = 0.4$ elsewhere. Table 3 shows the empirical sizes of the two competing testing procedures across the three distributional scenarios with $c = 10$. The proposed test seemed to preserve the nominal size but the Chen-Qin test appeared to have a highly inflated empirical size even when $r = 1000$, which prohibited us from conducting power comparisons.

3.3 Nominal size

Using $H_{\{c\}}$, $H_{\{[0.7c], [0.3c]\}}$ and $H_{\{[0.5c], [0.2c], [0.3c]\}}$, we examined in greater detail the size of the proposed methodology with non-independence dependence patterns. In particular, we assumed that $\Sigma = \Sigma_2 \otimes \Sigma_1$ where $\Sigma_1 = \{0.85^{|a-b|}\}_{1 \leq a, b \leq r}$ and $\Sigma_2 = 0.5(\mathbf{I}_c + \mathbf{J}_c)$ and we employed an exchangeable form for Σ but since the results were similar, we present only the simulations with the Kronecker product dependence structure. To reflect practical situations where the dimension of the mean vector is at least equal to the sample size (N) and the number of row variables (r) is greater or equal to the

Table 3: Empirical size of $H_{\{10\}}$ and the Chen-Qin test (with a Bonferroni correction) at 5% significance.

r	N	Scenario 1		Scenario 2		Scenario 3	
		$H_{\{10\}}$	Chen-Qin	$H_{\{10\}}$	Chen-Qin	$H_{\{10\}}$	Chen-Qin
100	10	0.048	0.179	0.066	0.179	0.065	0.173
	20	0.050	0.144	0.058	0.150	0.059	0.144
	30	0.059	0.147	0.069	0.157	0.056	0.158
	50	0.057	0.142	0.046	0.126	0.063	0.169
500	10	0.045	0.114	0.059	0.104	0.057	0.097
	20	0.051	0.115	0.046	0.090	0.054	0.091
	30	0.054	0.084	0.046	0.081	0.040	0.078
	50	0.054	0.091	0.050	0.090	0.050	0.077
1000	10	0.060	0.093	0.051	0.081	0.057	0.087
	20	0.053	0.080	0.059	0.068	0.046	0.090
	30	0.046	0.068	0.059	0.089	0.061	0.073
	50	0.042	0.067	0.051	0.075	0.052	0.067

number of column variables (c), we set $N = 10, 30, 50, 100$, $r = 100, 500, 1000$ and $c = 10, 100$. Also, we covered the case where the number of row variables is much smaller than the number of column variables by using $r = 10$ and $c = 100, 500$. Table 4 contains the empirical sizes under Scenario 3. Again, similar results were observed for the other two distributional scenarios, a fact that validates empirically the non-parametric nature of the methodology. The discrepancy between the empirical and nominal size was small for all three test statistics which confirms the robustness of the proposed testing procedure to the number of groups and to the group sizes.

3.4 Power considerations

Using $H_{\{c\}}$, $H_{\{[0.6c],[0.4c]\}}$ and $H_{\{[0.4c],[0.2c],[0.4c]\}}$, we also evaluated the empirical power of the proposed methodology under a multiplicative mean vectors scenario. In particular, we let $\mathbf{M} = [\mathbf{J}_{r \times [0.9c]}, t\mathbf{J}_{r \times [0.1c]}]$, where $t = 1.15$, $\Sigma_1 = \{0.85^{|a-b|}\}_{1 \leq a, b \leq r}$ and $\Sigma_2 = 0.5(\mathbf{I}_c + \mathbf{J}_c)$ for $r = 100, 500, 1000$ and $c = 10, 100$. Table 5 displays the simulation results based on $H_{\{c\}}$ across the three distributional scenarios. The tests based on $H_{\{[0.6c],[0.4c]\}}$ and $H_{\{[0.4c],[0.2c],[0.4c]\}}$ were more powerful and hence we do not show these results. Conditional on N , r and c , the empirical power was similar across the three distributional scenario and, as desired, it approached 1.00 as the sample size, the number of row or column variables increased.

4 Two Examples

We applied the proposed testing methodology to two datasets.

4.1 The glioblastoma dataset

The glioblastoma (GB) dataset describes an experimental study designed to explore the heterogeneity of GB (Sottoriva et al., 2013) by comparing the gene expression patterns in 3 different brain compartments; the tumor margin (MA), normal brain tissue that surrounds the tumor mass, the subventricular zone (SVZ), a targeted area located at the center of the brain, and the tumor mass. For each of the patients ($N = 8$) included in the study, 7 mRNA samples were extracted; 1 from the MA, 1 from the SVZ and 5 from different fragments in the tumor mass such that earlier fragments were closer to MA and later fragments closer to SVZ. Gene expression levels were then measured from the $7 \times 8 = 56$ mRNA samples using microarrays. The data for each subject were organized in a matrix with row variables ($r = 16810$) the genes and column variables ($c = 7$) the MA, the SVZ and the 5 tumor fragments ordered in the spatial order described above.

Table 4: Empirical size of the proposed methodology under Scenario 3 and a Kronecker product dependence structure at 5% significance.

N	r	$H_{\{c\}}$		$H_{\{[0.7c],[0.3c]\}}$		$H_{\{[0.5c],[0.2c],[0.3c]\}}$	
	c	10	100	10	100	10	100
10	100	0.064	0.056	0.059	0.056	0.057	0.058
	500	0.068	0.067	0.068	0.067	0.060	0.067
	1000	0.058	0.065	0.060	0.057	0.060	0.060
30	100	0.063	0.053	0.061	0.050	0.060	0.049
	500	0.049	0.054	0.053	0.048	0.049	0.049
	1000	0.049	0.057	0.048	0.063	0.056	0.056
50	100	0.058	0.046	0.059	0.048	0.064	0.048
	500	0.060	0.058	0.066	0.062	0.054	0.059
	1000	0.047	0.044	0.047	0.042	0.039	0.045
100	100	0.047	0.055	0.050	0.053	0.057	0.058
	500	0.047	0.048	0.049	0.040	0.048	0.044
	1000	0.051	0.068	0.055	0.068	0.051	0.067
	c	100	500	100	500	100	500
10	10	0.055	0.065	0.052	0.067	0.052	0.068
30	10	0.061	0.059	0.057	0.058	0.057	0.055
50	10	0.054	0.053	0.057	0.053	0.056	0.054
100	10	0.062	0.045	0.065	0.045	0.058	0.045

Table 5: Empirical power of $H_{\{c\}}$ for the multiplicity scenario at 5% significance.

	c	10	100	10	100	10	100
N	r	Scenario 1		Scenario 2		Scenario 3	
10	100	0.097	0.317	0.128	0.282	0.103	0.303
	500	0.210	0.778	0.207	0.813	0.206	0.781
	1000	0.331	0.967	0.305	0.971	0.315	0.965
30	100	0.291	0.975	0.313	0.964	0.294	0.966
	500	0.809	1.000	0.782	1.000	0.790	1.000
	1000	0.979	1.000	0.965	1.000	0.971	1.000
50	100	0.590	1.000	0.551	1.000	0.576	1.000
	500	0.997	1.000	0.992	1.000	0.998	1.000
	1000	1.000	1.000	1.000	1.000	1.000	1.000

An important biological hypothesis was the conservation of the mean vectors of gene expression levels across the tumor mass. Statistically speaking, this corresponds to testing the hypothesis

$$H_0 : \mathbf{M} = [\boldsymbol{\mu}_1, \boldsymbol{\mu}_2, \boldsymbol{\mu}_3 \mathbf{1}_5^T] \text{ vs. } H_1 : \text{ not } H_0, \quad (7)$$

where $\boldsymbol{\mu}_1$ and $\boldsymbol{\mu}_2$ denote the mean vector of gene expression levels in the MA and the SVZ respectively, and $\boldsymbol{\mu}_3$ denotes the common mean vector of gene expression levels in each of the 5 tumor fragments. The corresponding test statistic was equal to -0.282 (p -value = 0.611) suggesting that we did not have enough evidence to reject H_0 in (7). This motivated us to assess the likelihood of a simpler mean structure than the one tested in (7) (see Web Table 1). These results suggest that the overall gene expression patterns differed across the 3 brain compartments under study and thus, $\mathbf{M} = [\boldsymbol{\mu}_1, \boldsymbol{\mu}_2, \boldsymbol{\mu}_3 \mathbf{1}_5^T]$ described adequately the compartment-wise mean relationship in the GB dataset.

We compared further the mean gene expression patterns in the MA and the tumor mass by utilizing Gene Ontology (GO) terms. The GO terms classify genes into groups such that the genes within a group are involved in the same biological process. From the 1316 gene groups in the GB dataset, we selected 231 groups that had more than 7 genes in order to be closer to the high-dimensional assumptions. For the k -th group of genes ($k = 1, \dots, 231$) with mean matrix \mathbf{M}_k , we tested the hypothesis

$$H_{0k} : \mathbf{M}_k = [\boldsymbol{\mu}_{1k}, \boldsymbol{\mu}_{2k}, \boldsymbol{\mu}_{1k} \mathbf{1}_5^T] \text{ vs. } H_{1k} : \text{ not } H_{0k},$$

where $\boldsymbol{\mu}_{1k}$ denotes the common mean gene expression levels vector in the MA and in the 5 tumor fragments, and $\boldsymbol{\mu}_{2k}$ denotes the mean gene expression levels vector in the SVZ. After applying an FDR correction, we rejected the null hypothesis in 224 groups. The high-proportion of rejections (96.97%) supports the adopted form for the overall mean matrix \mathbf{M} . Many of these 224 gene-groups correspond to biological processes that are known to be directly linked to cancer, including cellular response to hypoxia and the extracellular matrix organization (Gilkes et al., 2014), negative regulation of retinoic acid receptor signaling pathway (Tang and Gudas, 2011; Connolly et al., 2013) and positive regulation of ERK1 and ERK2 cascade (Santamaria and Nebreda, 2010) among others. Thus, rejecting the corresponding H_{0k} can be biologically justified.

4.2 The mouse aging dataset

The atlas of gene expression in the mouse aging data (Zahn et al., 2007) contains mouse mRNA gene expression levels measured in different tissues. For each mouse ($N = 40$), mRNA expression levels were extracted for $r = 8932$ genes from up to 16 tissues. Here, we considered $c = 9$ tissues (adrenal glands, cerebrum, hippocampus, kidney, lung, muscle, spinal cord, spleen and thymus) for which mRNA gene expression levels were available for all the mice.

Unsurprisingly, the hypothesis of no tissue effect upon the mean expression level was rejected since $G_N^* = 481.28$ (p -value < 0.001). A subset of genes called ‘housekeeping’ genes are typically assumed to be expressed at a relatively constant level across many or all known experimental conditions. As a result, these genes are often used to calibrate gene expression levels across experiments. However, it has been suggested that commonly used housekeeping genes can show considerable variability in expression across tissues (de Jonge et al., 2007; Kouadjo et al., 2007). To explore this, we created a list of 22 housekeeping genes compromised of 8 genes that are commonly classified as housekeeping genes (de Jonge et al., 2007) and 14 genes that were classified as housekeeping genes by de Jonge et al. (2007). The hypothesis of conservation of the mean expression levels of this gene-set across the 9 tissues was rejected ($G_N^* = 382.93$ and p -value < 0.001). We believe that further research is required in order to identify housekeeping genes for these 9 tissues and the proposed testing methodology is a useful statistical tool to this direction.

5 Discussion

We proposed a novel non-parametric procedure to test the mean matrix in high-dimensional transposable data. In particular, our methodology can determine whether in each of the given groups of column variables the mean of every row variable remains constant. Of course, the role of the row and column

variables is interchangeable in transposable data and hence the proposed tests can be applied to check the effect of the row variables upon the mean vector of the column variables. The simulation studies verified the robustness of the proposed testing procedure to the number of row or column groups, to the size of each group, to the number of column and row variables relative to the sample size, and to the underlying dependence structure between and among the row and column variables. In simulations, the proposed tests were more powerful than univariate testing procedures that require row-wise and/or column-wise independence in almost all settings. In a sense, we developed a theoretically sound non-parametric testing procedure that extends the application of univariate ANOVA flavored tests to high-dimensional transposable data while making mild dependence structure assumptions. The practical advantage of the proposed test is its computational simplicity since the cumbersome task of estimating high-dimensional matrix parameters, such as the mean matrix and the covariance matrix, is avoided. The proposed testing methodology is implemented in the function *meanmat.ts()* of the R package HDTD (available at <http://www.bioconductor.org/packages/3.0/bioc/html/HDTD.html>).

In practice, we expect that the experimental design will dictate the null hypothesis of interest about the mean-relationship between the row and column variables, as was the case with the glioblastoma dataset. In applications where it is not clear which column (or row) groups should be formed under the null hypothesis, the following strategy that can be helpful in determining the column-wise (row-wise) structure. First, test whether there is no column (row) effect upon the mean of the row (column) variables. If we fail to reject this hypothesis, assume that the mean of the row (column) variables is independent of the column (row) variables. Otherwise, perform the test that two column (row) variables have the same mean vector for all pairs of column (row) variables, and then adjust for multiple testing using an FDR or a Bonferroni correction. If all the adjusted p -values are very small, then assume an unstructured mean matrix \mathbf{M} or transpose the data and repeat the above procedure for the column (row) variables. Otherwise, record the column (row) pairs for which the adjusted p -values < 0.05 , form g column (row) groups and test hypothesis (2) as this is determined by the g groups.

In future work, we aim to develop test statistics for hypotheses that cannot be directly handled by the proposed testing methodology, e.g. the hypothesis of a mean-restricted matrix (Allen and Tibshirani, 2010), that is $\mathbf{M} = \boldsymbol{\mu}\mathbf{1}_c^T + \mathbf{1}_r\boldsymbol{\nu}^T$ where $\boldsymbol{\mu}$ is an r -variate vector of constants and $\boldsymbol{\nu}$ is a c -variate vector of constants, and hypotheses of testing simultaneously the presence of predefined row and column groups.

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Supplementary Material: Testing the Mean Matrix in High-Dimensional Transposable Data

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Web Appendix A: Proof of Theorem 1

Without loss of generality, let \mathbf{P} be an idempotent and symmetric matrix that satisfies condition (4) and either condition (5) or condition (6). Define $\mathbf{Y}_i = \text{vec}(\mathbf{X}_i \mathbf{P})$ for all i , where $E[\mathbf{Y}_i] = \text{vec}(\mathbf{M} \mathbf{P})$ and $\text{cov}[\mathbf{Y}_i] = \mathbf{\Omega} = (\mathbf{P} \otimes \mathbf{I}_r) \mathbf{\Sigma} (\mathbf{P} \otimes \mathbf{I}_r)$. Rewrite relations (4), (5) and (6) as

$$\begin{aligned} \text{tr}(\mathbf{\Omega}^4) &= o\{\text{tr}^2(\mathbf{\Omega}^2)\}, \\ \text{vec}(\mathbf{M})^T \mathbf{\Omega} \text{vec}(\mathbf{M}) &= o\{\text{tr}(\mathbf{\Omega}^2)/N\} \end{aligned}$$

and

$$\text{tr}(\mathbf{\Omega}^2)/N = o\{\text{vec}(\mathbf{M})^T \mathbf{\Omega} \text{vec}(\mathbf{M})\}$$

respectively, and note that

$$G_N = \frac{1}{N(N-1)} \sum_{i \neq j} \text{tr}(\mathbf{X}_i^T \mathbf{X}_j \mathbf{P}) = \frac{1}{N(N-1)} \sum_{i \neq j} \mathbf{Y}_i^T \mathbf{Y}_j.$$

With this parameterization, the asymptotic distribution of $(G_N - E[G_N])/\sqrt{\text{Var}[G_N]}$ can be derived in a similar fashion as in the proof of Theorem 1 in Chen and Qin (2010).

Web Appendix B: Additional Simulation Results

Web Table 2 displays the empirical size of the ANOVA test and the Kruskal-Wallis test in the presence of row-wise and column-wise dependence. In particular, it was assumed that $\mathbf{\Sigma} = \mathbf{\Sigma}_2 \otimes \mathbf{\Sigma}_1$ where $\mathbf{\Sigma}_1 = \{0.85^{|a-b|}\}_{1 \leq a, b \leq r}$ and $\mathbf{\Sigma}_2 = 0.5(\mathbf{I}_c + \mathbf{J}_c)$ so that the results are comparable to those in Table 4. Unlike to the proposed testing methodology, the nominal size was not preserved for the univariate tests. In fact, the ANOVA test and the Kruskal-Wallis test failed to reject the null hypothesis throughout this sampling scheme. This suggests that practical approaches might not be suitable to use with high-dimensional transposable data.

Moreover, we considered the empirical power of the competing testing procedures (proposed tests, ANOVA and Kruskal-Wallis approaches) under a sparsity scenario for the mean structure, $\mathbf{M} = [\mathbf{0}_{r \times 9}, \boldsymbol{\mu}]$, and with an equal allocation for the varying proportion (0%, 25%, 50%, 75%, 95% and 99%) of zero elements in $\boldsymbol{\mu}$. We set $r = 100, 500, 1000$ and we let $\mathbf{\Sigma} = \mathbf{I}_{10r}$. To make the results comparable across the sampling schemes, the non-zero elements of $\boldsymbol{\mu}$ were defined in such a way that

$$\frac{\text{tr}(\mathbf{M}^T \mathbf{M})}{\sqrt{r(c-1)}} = 0.15.$$

Web Table 4 displays the simulation results only for $r = 1000$ under Scenario 3 because we observed similar trends for the other 8 sampling schemes. The same conclusions as those with an increasing allocation (see Table 2) can be drawn. Therefore, the empirical power of the proposed test did not seem to be affected by the type of allocation of the non-zero elements in $\boldsymbol{\mu}$.

We considered a sparsity scenario for the mean matrix configuration under non-independence of the row and column variables. We evaluated the empirical power of the proposed testing methodology via $H_{\{c\}}$, $H_{\{[0.6c],[0.4c]\}}$ and $H_{\{[0.4c],[0.2c],[0.4c]\}}$. We defined $\mathbf{M} = [\mathbf{0}_{r \times [0.7c]}^T, \boldsymbol{\mu} \mathbf{1}_{[0.3c]}^T]$ and similarly to Chen and Qin (2010), we let $\boldsymbol{\mu}$ contain a varying proportion (0%, 25%, 50%, 75%, 95% and 99%) of zero elements. At each proportion level, we employed two types of allocations for the non-zero elements: (i) equal allocation and (ii) linearly increasing allocation where two nonzero-elements of $\boldsymbol{\mu}$ satisfy $\mu_{l_1} < \mu_{l_2}$ if and only if $l_1 < l_2$. We set $r = 100$, $c = 10$ and we used a Kronecker product form for $\boldsymbol{\Sigma}$ with $\boldsymbol{\Sigma}_1 = \{0.8^{|a-b|}\}_{1 \leq a, b \leq r}$ and $\boldsymbol{\Sigma}_2 = 0.5(\mathbf{I}_c + \mathbf{J}_c)$. To make the results comparable across the different proportion levels, the non-zero elements of $\boldsymbol{\mu}$ were defined in such a way that

$$\frac{\text{tr}(\mathbf{M}^T \mathbf{M})}{\sqrt{\text{tr}(\boldsymbol{\Sigma}_1^2) \text{tr}(\boldsymbol{\Sigma}_2^2)}} = 0.1.$$

Table 4 displays the simulation results for $H_{\{6,4\}}$. Similar trends occurred for $H_{\{4,2,4\}}$ but not for $H_{\{10\}}$, which was extremely powerful in these settings. This indicates that as we move away from H_0 , the power of the proposed methodology increases. Conditional on the sample size, the empirical power was similar across the three distributional scenario and it did not depend on the type of allocation or the proportion level. The proposed testing procedure was powerful to the sparsity scenarios considered and their empirical power approached 1.00 as N increased.

Finally, we increased $r = 10,000$ and we let $c = 1000$, $N = 10, 30, 50$ and $\boldsymbol{\Sigma} = \mathbf{I}_{10r}$ under Scenario 3. For the mean structure, we assumed the same configuration as in Table 2. In addition we calculated the empirical size. The results for the proposed method are displayed in Web Table 5. Clearly, increasing r does not affects the conclusions drawn in Table 2 as long as we keep

$$\frac{\text{tr}(\mathbf{M}^T \mathbf{M})}{\sqrt{r(c-1)}}$$

fixed.

Web Appendix C: Class of Covariance Matrices under Consideration

Let $\lambda_k(\boldsymbol{\Delta})$ denote the k -th ordered eigenvalue of a $p \times p$ symmetric matrix $\boldsymbol{\Delta}$ such that

$$\lambda_{rc}(\boldsymbol{\Delta}) \leq \lambda_{rc-1}(\boldsymbol{\Delta}) \leq \dots \leq \lambda_1(\boldsymbol{\Delta}),$$

and recall that

$$\mathbf{P} = \mathbf{P}_{\{c_1, c_2, \dots, c_g\}} = \mathbf{I}_c - \text{diag}(\mathbf{J}_{c_1}/c_1, \mathbf{J}_{c_2}/c_2, \dots, \mathbf{J}_{c_g}/c_g) = \mathbf{I}_c - \mathbf{H}_c$$

where the integers $\{c_1, \dots, c_g\}$ satisfy the constraint $c_1 + c_2 + \dots + c_g = c$.

Suppose that $\boldsymbol{\Sigma} = \boldsymbol{\Sigma}_2 \otimes \boldsymbol{\Sigma}_1$ in which case

$$\frac{\text{tr}(\boldsymbol{\Omega}^4)}{\text{tr}^2(\boldsymbol{\Omega}^2)} = \frac{\text{tr}[(\mathbf{P}\boldsymbol{\Sigma}_2)^4]}{\text{tr}^2[(\mathbf{P}\boldsymbol{\Sigma}_2)^2]} \frac{\text{tr}(\boldsymbol{\Sigma}_1^4)}{\text{tr}^2(\boldsymbol{\Sigma}_1^2)}.$$

If $\text{tr}(\boldsymbol{\Sigma}_1^4) = o\{\text{tr}^2(\boldsymbol{\Sigma}_1^2)\}$, then condition (4) is satisfied. Now we prove that condition (4) is also met when $\text{tr}(\boldsymbol{\Sigma}_2^4) = o\{\text{tr}^2(\boldsymbol{\Sigma}_2^2)\}$. First, note that

$$\frac{\lambda_1^4(\boldsymbol{\Sigma}_2)}{\text{tr}^2(\boldsymbol{\Sigma}_2^2)} \leq \frac{\sum_{k=1}^{rc} \lambda_k^4(\boldsymbol{\Sigma}_2)}{\text{tr}^2(\boldsymbol{\Sigma}_2^2)} = \frac{\text{tr}(\boldsymbol{\Sigma}_2^4)}{\text{tr}^2(\boldsymbol{\Sigma}_2^2)},$$

and thus the condition $\text{tr}(\mathbf{\Sigma}_2^4) = o\{\text{tr}^2(\mathbf{\Sigma}_2^2)\}$ implies that $\lambda_1(\mathbf{\Sigma}_2) = o\left\{\sqrt{\text{tr}(\mathbf{\Sigma}_2^2)}\right\}$. Now write

$$\text{tr}[(\mathbf{P}\mathbf{\Sigma}_2)^2] = \text{tr}(\mathbf{\Sigma}_2^2) + \text{tr}(\mathbf{H}_c\mathbf{\Sigma}_2\mathbf{H}_c\mathbf{\Sigma}_2) - 2\text{tr}(\mathbf{H}_c\mathbf{\Sigma}_2^2)$$

and note that

$$0 \leq \text{tr}(\mathbf{H}_c\mathbf{\Sigma}_2\mathbf{H}_c\mathbf{\Sigma}_2) \leq \text{tr}(\mathbf{H}_c\mathbf{\Sigma}_2^2) \leq \sum_{k=1}^g \lambda_k(\mathbf{H}_c)\lambda_k(\mathbf{\Sigma}_2^2) \leq \sum_{k=1}^g \lambda_k^2(\mathbf{\Sigma}_2) \leq g\lambda_1^2(\mathbf{\Sigma}_2).$$

It follows that

$$\frac{\text{tr}[(\mathbf{P}\mathbf{\Sigma}_2)^2]}{\text{tr}(\mathbf{\Sigma}_2^2)} \rightarrow 1$$

and hence

$$\frac{\text{tr}[(\mathbf{P}\mathbf{\Sigma}_2)^4]}{\text{tr}^2[(\mathbf{P}\mathbf{\Sigma}_2)^2]} \rightarrow 0.$$

The above prove that $\mathbf{\Sigma}_1$ and/or $\mathbf{\Sigma}_2$ belong to the class of covariance matrices $\mathbf{\Delta}$ for which $\text{tr}(\mathbf{\Delta}^4) = o\{\text{tr}^2(\mathbf{\Delta}^2)\}$. This class includes covariance matrices that have bounded eigenvalues or have a few eigenvalues that diverge slowly to infinity (Chen and Qin, 2010) or when $\mathbf{\Sigma}_1$ and $\mathbf{\Sigma}_2$ a (banded) first order autoregressive correlation pattern such that the variances are bounded away from 0 or ∞ (Chen et al., 2010). Under the Kronecker product structure, when $c \rightarrow \infty$ and $\mathbf{\Sigma}_2$ satisfies a compound symmetry correlation matrix, i.e., $\mathbf{\Sigma}_2 = \rho\mathbf{I}_c + (1 - \rho)\mathbf{J}_c$ for $-1/(c - 1) < \rho \leq 1$, it can be shown that

$$\frac{\text{tr}(\mathbf{\Omega}^4)}{\text{tr}^2(\mathbf{\Omega}^2)} \leq \frac{\text{tr}[(\mathbf{P}\mathbf{\Sigma}_2)^4]}{\text{tr}^2[(\mathbf{P}\mathbf{\Sigma}_2)^2]} = \frac{(1 - \rho)^4(c - g)}{[(1 - \rho)^2(c - g)]^2} \rightarrow 0.$$

Next, suppose that the column variables are uncorrelated, in which case $\mathbf{\Sigma}$ is a block diagonal matrix and $\text{tr}(\mathbf{\Sigma}^4) = o\{\text{tr}^2(\mathbf{\Sigma}^2)\}$. We prove that condition (4) holds when $\mathbf{H}_c = \mathbf{J}_c/c$. The proof is similar when $\mathbf{H}_c = \text{diag}(\mathbf{J}_{c_1}/c_1, \mathbf{J}_{c_2}/c_2, \dots, \mathbf{J}_{c_g}/c_g)$. Let $\mathbf{H} = \mathbf{H}_c \otimes \mathbf{I}_r$. Some algebra shows that $\text{tr}(\mathbf{H}\mathbf{\Sigma}^2) = \text{tr}(\mathbf{\Sigma}^2)/c$ and $\text{tr}(\mathbf{H}\mathbf{\Sigma}\mathbf{H}\mathbf{\Sigma}) > \text{tr}(\mathbf{\Sigma}^2)/c^2$, and consequently

$$\text{tr}(\mathbf{\Omega}^2) = \text{tr}(\mathbf{\Sigma}^2) + \text{tr}(\mathbf{H}\mathbf{\Sigma}\mathbf{H}\mathbf{\Sigma}) - 2\text{tr}(\mathbf{H}\mathbf{\Sigma}^2) \geq (1 - 1/c)^2\text{tr}(\mathbf{\Sigma}^2) \geq \text{tr}(\mathbf{\Sigma}^2)/2.$$

Therefore

$$\frac{\text{tr}(\mathbf{\Omega}^4)}{\text{tr}^2(\mathbf{\Omega}^2)} \leq 4\frac{\text{tr}(\mathbf{\Sigma}^4)}{\text{tr}^2(\mathbf{\Sigma}^2)} \rightarrow 0.$$

Finally, assume that neither the rows nor the columns are independent. By the Pioncare separation theorem, it follows that

$$\lambda_{rg+k}(\mathbf{\Sigma}) \leq \lambda_k(\mathbf{\Omega}) \leq \lambda_k(\mathbf{\Sigma})$$

for $k = 1, \dots, r(c - g)$ and that $\lambda_{r(c-g)+1}(\mathbf{\Omega}) = \dots = \lambda_{rc}(\mathbf{\Omega}) = 0$. Assume first that $\mathbf{\Sigma}$ has eigenvalues bounded away from zero and infinity, i.e., there exist constants L and U such that

$$0 < L \leq \lambda_{rc}(\mathbf{\Sigma}) \leq \dots \leq \lambda_1(\mathbf{\Sigma}) \leq U < \infty$$

then

$$\frac{\text{tr}(\mathbf{\Omega}^4)}{\text{tr}^2(\mathbf{\Omega}^2)} \leq \frac{1}{r(r - g)} \frac{U^4}{L^4} \rightarrow 0$$

as $rc \rightarrow \infty$. It can be shown that condition (4) holds even if $\mathbf{\Sigma}$ has unbounded eigenvalues with $\lambda_1(\mathbf{\Sigma}) \rightarrow \infty$ and $\lambda_{rc}(\mathbf{\Sigma}) \rightarrow 0$ such that $\lambda_1(\mathbf{\Sigma}) = o\{r(c - g)\lambda_{rc}(\mathbf{\Sigma})\}$. Next assume that $\mathbf{\Sigma} = \rho\mathbf{I}_{rc} + (1 - \rho)\mathbf{J}_{rc}$ for $-1/(rc - 1) < \rho \leq 1$. For all $k = 1, 2, \dots$, it can be readily shown that $\text{tr}(\mathbf{\Omega}^k) = (1 - \rho)^k r(c - g)$ and thus condition (4) is met. Consider the case where $\mathbf{\Sigma}$ satisfies a first order autoregressive correlation matrix and $\mathbf{H}_c = \mathbf{J}_c/c$. Similar arguments generalize the result for $\mathbf{H}_c = \text{diag}(\mathbf{J}_{c_1}/c_1, \mathbf{J}_{c_2}/c_2, \dots, \mathbf{J}_{c_g}/c_g)$. It can be shown that $\text{tr}(\mathbf{H}_c\mathbf{\Sigma}^2) = o\{\text{tr}(\mathbf{H}_c\mathbf{\Sigma}^2)\}$ which implies condition (4).

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WebTable 1: Hypothesis testing results regarding the global mean structure in the GB study.

Mean matrix under H_0	Test statistic	p -value	
		Unadjusted	FDR correction
$\mathbf{M} = [\boldsymbol{\mu}_1, \boldsymbol{\mu}_2, \boldsymbol{\mu}_3 \mathbf{1}_5^T]$	-0.2818	0.6110	0.6110
$\mathbf{M} = [\boldsymbol{\mu}_1, \boldsymbol{\mu}_1, \boldsymbol{\mu}_3 \mathbf{1}_5^T]$	15.2426	<0.0001	<0.0001
$\mathbf{M} = [\boldsymbol{\mu}_1, \boldsymbol{\mu}_2, \boldsymbol{\mu}_2 \mathbf{1}_5^T]$	3.0211	0.0013	0.0016
$\mathbf{M} = [\boldsymbol{\mu}_1, \boldsymbol{\mu}_2, \boldsymbol{\mu}_1 \mathbf{1}_5^T]$	22.2515	<0.0001	<0.0001
$\mathbf{M} = [\boldsymbol{\mu}_1, \boldsymbol{\mu}_1, \boldsymbol{\mu}_1 \mathbf{1}_5^T]$	22.5101	<0.0001	<0.0001

WebTable 2: Empirical sizes of ANOVA and Kruskal-Wallis test under Scenario 3 and under a Kronecker product dependence structure at 5% significance.

N	r	ANOVA		Kruskal-Wallis	
		FDR	BON	FDR	BON
10	100	0.000	0.000	0.000	0.000
	500	0.000	0.000	0.000	0.000
30	100	0.000	0.000	0.000	0.000
	500	0.000	0.000	0.000	0.000
50	100	0.000	0.000	0.000	0.000
	500	0.000	0.000	0.000	0.000
100	100	0.000	0.000	0.000	0.000
	500	0.000	0.000	0.000	0.000

WebTable 3: Empirical power of $H_{\{10\}}$, ANOVA and Kruskal-Wallis for the sparsity scenario with $r = 1000$ under Scenario 3 under an equal allocation at 5% significance

N	$\#\{\mu_l = 0\}$	$H_{\{10\}}$	ANOVA		Kruskal-Wallis	
			FDR	BON	FDR	BON
10	99%	0.181	0.214	0.203	0.052	0.051
	95%	0.194	0.075	0.074	0.006	0.006
	75%	0.193	0.063	0.062	0.003	0.003
	50%	0.186	0.064	0.061	0.004	0.004
	25%	0.187	0.063	0.058	0.003	0.003
	0 %	0.186	0.060	0.058	0.003	0.003
20	99%	0.703	1.000	1.000	1.000	1.000
	95%	0.709	0.287	0.273	0.189	0.177
	75%	0.696	0.090	0.089	0.050	0.046
	50%	0.707	0.076	0.075	0.041	0.040
	25%	0.699	0.080	0.077	0.045	0.045
	0 %	0.693	0.080	0.076	0.049	0.048
50	99%	0.974	1.000	1.000	1.000	1.000
	95%	0.975	0.786	0.739	0.677	0.641
	75%	0.976	0.160	0.149	0.122	0.117
	50%	0.976	0.123	0.117	0.093	0.089
	25%	0.977	0.116	0.115	0.089	0.086
	0 %	0.976	0.108	0.105	0.088	0.086
100	99%	1.000	1.000	1.000	1.000	1.000
	95%	1.000	1.000	1.000	1.000	1.000
	75%	1.000	0.444	0.401	0.372	0.336
	50%	1.000	0.235	0.209	0.198	0.185
	25%	1.000	0.197	0.185	0.177	0.169
	0 %	1.000	0.176	0.164	0.168	0.158

WebTable 4: Empirical power of $H_{\{6,4\}}$ for the sparsity scenario with $r = 100$ at 5% significance.

N	$\#\{\mu_l = 0\}$	Equal Allocation			Increasing Allocation		
		Scenario 1	Scenario 2	Scenario 3	Scenario 1	Scenario 2	Scenario 3
10	99%	0.194	0.213	0.173	0.194	0.213	0.173
	95%	0.175	0.207	0.164	0.172	0.213	0.163
	75%	0.166	0.204	0.171	0.168	0.205	0.173
	50%	0.174	0.211	0.169	0.172	0.207	0.169
	25%	0.173	0.203	0.170	0.169	0.203	0.168
	0%	0.167	0.201	0.165	0.164	0.199	0.166
30	99%	0.605	0.609	0.606	0.605	0.609	0.606
	95%	0.626	0.582	0.605	0.623	0.589	0.605
	75%	0.632	0.634	0.635	0.637	0.637	0.642
	50%	0.643	0.646	0.649	0.651	0.648	0.650
	25%	0.645	0.647	0.654	0.647	0.645	0.653
	0%	0.658	0.644	0.663	0.662	0.643	0.666
50	99%	0.903	0.868	0.882	0.903	0.868	0.882
	75%	0.896	0.897	0.899	0.904	0.898	0.896
	50%	0.938	0.936	0.934	0.947	0.941	0.936
	25%	0.962	0.955	0.949	0.965	0.958	0.954
	5%	0.964	0.959	0.954	0.967	0.964	0.958
	0%	0.965	0.966	0.961	0.969	0.967	0.963

WebTable 5: Empirical size and power of $H_{\{10\}}$ for the sparsity scenario with $r = 10000$ under Scenario 3 at 5% significance

N	$\#\{\mu_l = 0\}$	Scenario 1	Scenario 2	Scenario 3
10	100%	0.055	0.056	0.068
	99%	0.181	0.158	0.166
	95%	0.176	0.159	0.164
	75%	0.178	0.151	0.164
	50%	0.180	0.158	0.170
	25%	0.181	0.163	0.169
	0%	0.182	0.164	0.166
30	100%	0.050	0.054	0.065
	99%	0.660	0.591	0.664
	95%	0.653	0.599	0.660
	75%	0.653	0.586	0.644
	50%	0.656	0.592	0.650
	25%	0.649	0.588	0.661
	0%	0.648	0.596	0.650
50	100%	0.050	0.055	0.039
	99%	0.952	0.952	0.953
	95%	0.948	0.954	0.943
	75%	0.953	0.953	0.944
	50%	0.952	0.954	0.947
	25%	0.955	0.956	0.947
	0%	0.954	0.954	0.952